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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/764,163	01/16/2001	Robert F. Balint	PARE.002.02US	7613

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TOWNSEND AND TOWNSEND AND CREW, LLP  
TWO EMBARCADERO CENTER  
EIGHTH FLOOR  
SAN FRANCISCO, CA 94111-3834

EXAMINER

PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/764,163

Applicant(s)

BALINT ET AL.

Examiner

Padmashri Ponnaluri

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 March 2004 and 29 August 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 80-89 is/are pending in the application.
- 4a) Of the above claim(s) 89 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 80-88 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 8/7/01 and 11/30/01 & 5/9/01
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. The amendment filed on 8/29/03 has been fully considered and entered into the application.
2. Claims 1-79 have been canceled and new claims 80-89 have been added by the amendment filed on 8/29/03.
3. Claims 80-89 are currently pending in this application.
4. Applicant's election of group 14 (original claims 27, 34-38 and 40-46), a fusion protein in Paper filed on 12/16/02 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants have canceled the elected claims, and added new set of fusion proteins by the amendment filed on 8/29/03. During a telephonic Interview (7/14/03) with Examiner Epperson, it was agreed that new claims 80-88 will be examined as elected group, and further species election was requested by fax on 12/16/02.

Applicants in the response filed on 8/29/03 have elected without traverse species election of the following: beta-lactamase is TEM-1; junction is E197 and L198. And further it is noted that applicants have elected Subgroup 14: fusion protein comprised of bacterial signal peptide, linker (Gly4Ser)3; and subgroups 15, 16, 21, 22, 23, which are not found in the elected or currently present claims.

5. Claim 89 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed on 8/29/03.

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6. Claims 80-88 are currently being examined in this application.

***Priority***

7. This application claims priority to provisional application 60/175,968 and this application is a CIP of 09/526,106.

8. Claims 80-88 may not have the benefit of the filing date of the parent application serial number 09/526,106 (filing date 3/15/00). The 'ligand activated uni-molecular detector' claimed in Claims 80-88 has no clear support in parent application serial number 09/526,106. Thus the instant claims has the effective filing date of the instant application filing date 1/16/01.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

9. Claims 85-86 (in-part) may not have the benefit of the filing date of the parent application serial number 09/526,106 (filing date 3/15/00). The N-terminal and C-terminal break points in the circularly permuted  $\beta$ -lactamase, asparagine 52 and serine 53; leucine and glycine 92; glutamine 99 and asparagine 100; ; lysine 215 and valine; and alanine 227 and glycine 228' claimed in Claims 85-86 has no clear support in parent application serial number 09/526,106. Thus the instant claims has the effective filing date of the instant application filing date 1/16/01.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

***Information Disclosure Statement***

10. The information disclosure statements filed on 5/9/01, 8/7/01 and 11/30/01 have been fully considered.

***Specification***

11. The disclosure is objected to because of the following informalities: in page 1, line 14, blank spaces for the 'grant number' and 'awarded by' are noticed.

Appropriate correction is required.

The specification has not checked to the extent necessary to determine the presence of all possible minor errors. Applicant's co-operation is requested in correcting any errors of which applicant may become aware in the specification.

***Claim Rejections - 35 USC § 112***

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 80-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The 'ligand activated uni-molecular detector' claimed in Claims 80-88 has no clear

support in the specification and the claims as originally filed. The subject matter claimed in claims uni-molecular detector broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

14. Claims 80-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants instant claim 80 is drawn to a ligand-activated uni-molecular detector comprising: a circularly permuted marker protein, first interactor domain covalently bonded to N-terminal, and second interactor domain covalently bonded to the C-terminal of the circularly permuted marker, and the circularly permuted marker protein is functionally reconstituted only upon binding of said interactor domain and second interactor domain to a single ligand. And claim 85 recites that the circularly permuted marker protein consists essentially of  $\beta$ -lactamase protein of SEQ ID NO:2.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise

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definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. For adequate disclosure, representative examples are required, which provides reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had in possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *in re Barr* (CCPA 1971) 444F2d 349, 151 US PQ 724 and *University of California v. Eli Lilly and Co.*

The instant specification discloses the circularly permuted  $\beta$ -lactamase which is covalently linked to either antibody fragments or thioredoxin (interacting domains), which clearly does not provide an adequate representation regarding the open ended uni-molecular detector of the instant claim 80. And further applicants have not disclosed the analogues of the SEQ ID NO:2, which is used in the claimed invention (claim 85 recites 'consists essentially of', which is open to other modification by addition or substitutions to the sequence). Thus, the specification has not provided 'representative number of examples' that would indicate to an ordinary skill in the art that applicant had possession of the broadly claimed uni-molecular detector.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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16. Claims 80-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 80 is vague and indefinite by reciting 'ligand-activated uni-molecular detector', it is not clear what does applicants mean by uni-molecular detector. Since the instant detector has circularly permuted marker protein, and two other interacting domains and the ligand bound together, it is not clear what does applicants mean by 'uni-molecular.'

The instant claim 80 recites 'a circularly permuted marker comprising a first interactor domain....and a second interactor domain...' It is not clear what does applicants mean by 'circularly permuted marker comprising...', does applicants mean that the marker originally circularly permuted or upon the covalent bonding of the first interactor and second interactor the marker protein is circular. Applicants are requested to clarify.

The instant claim 80 recites 'a ligand activated uni-molecular detector', does applicants mean that the claimed detector has the circularly permuted marker protein bound to interactor domains and a ligand (i.e., a composition comprising circularly permuted marker protein bound to interactor domains and a ligand) or the ligand is not present in the claimed composition. Applicants are requested to clarify the components present in the claimed composition.

Claim 85 is vague and indefinite by reciting 'consists essentially of a  $\beta$ -lactamase protein.' The term consists essentially of is a open term, which may include analogues or variations or derivatives of the lactamase. However, the specification has no clear examples of these compounds.



***Claim Rejections - 35 USC § 102***

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 80-81 are rejected under 35 U.S.C. 102(b) as being anticipated by Remy et al (Proc. Natl. Acad. Sci. USA, vol. 96, pp 5394-5399, May 1999).

Briefly instant claims are drawn to a ligand-activated uni-molecular detector comprising: a circularly permuted marker protein, first interactor domain covalently bonded to N-terminal, and second interactor domain covalently bonded to the C-terminal of the circularly permuted marker, and the circularly permuted marker protein is functionally reconstituted only upon binding of said interactor domain and second interactor domain to a single ligand.

Remy et al teach protein complementation assay. The reference a clonal selection assay of stably transfected cells expressing partner proteins FKBP and FRAP (refers to the first and second interacting domains of the instant claims) fused to DHFR fragments (refers to the circularly permuted marker protein of the instant claims) and show rapamycin (refers to the ligand of the instant claims) dependent survival of clones. The reference figure depicts the

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FKBP-rapamycin-FRB complex fused the DHFR. Thus the reference clearly anticipates the claimed invention.

19. Claims 80-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Pieper et al (Biochemistry, 1997, 36, 8767-8774) (reference provided by applicants).

Briefly instant claims are drawn to a ligand-activated uni-molecular detector comprising: a circularly permuted marker protein, first interactor domain covalently bonded to N-terminal, and second interactor domain covalently bonded to the C-terminal of the circularly permuted marker, and the circularly permuted marker protein is functionally reconstituted only upon binding of said interactor domain and second interactor domain to a single ligand.

NOTE the recitation of the 'ligand activated' is considered as product by process limitation. The instant claims have been considered as composition/or compound comprising a marker protein, which is covalently bonded to interactor domains to form a circularly permuted marker protein, which is functionally active.

Pieper et al teach circularly permuted  $\beta$ -lactamase (refers to the circularly permuted marker protein of the instant claims). The reference teaches that in a circularly permuted protein the N- and C- termini of the native protein have been joined and new termini introduced somewhere else along the polypeptide chain. The reference teaches that two circularly permuted proteins have been produced, one construct was cleaved before position 228 (cp228  $\beta$ -lactamase), and the second construct is cleaved at the position 254 (cp254 $\beta$ -lactamase) (refers to the break points of the instant claims 85 and 86). The reference teaches that an eight residue long peptide (refers to the first and second interactor domain of the instant claims) joins the N- and C-terminal helices of the native molecule (refers to the covalently bonded first interactor domain to

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the N-terminal breakpoint and second interactor domain bonded to the C-terminal break point of the circularly permuted marker protein of the instant claims). The reference teaches that the eight-residue insertion incorporated into the circularly permuted genes were intended to mimic the conformation of the connecting loop in glucose oxidase and to extend the N-terminal helix of the native molecule by half turn by analogy to glucose oxidase. The reference teaches that both cp228 and cp-254  $\beta$ -lactamase) are enzymatically active (refers to the functionally reconstituted marker of the instant claims). The reference clearly anticipates the claimed invention.

20. Claims 80-81 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,270,964 B1 (Michnick et al) (reference provided by applicants)

Michnick et al teach protein fragment complementation assay for detection of biological or drug interactions. The reference teaches that reconstitution of enzyme activity only occurs when the N- and C-terminal fragments of DHFR (refers to instant circularly permuted marker protein) were co-expressed as C-terminal fusion of GCN4 leucine zipper sequences (refers to the interactor domains of the instant claims). Thus, the reference clearly anticipates the instant claims.

### ***Double Patenting***

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 80-88 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-66 of copending Application No. 09526,106. Although the conflicting claims are not identical, they are not patentably distinct from each other because the reference application claims are drawn to 'an oligopeptide consisting essentially of an N-terminal  $\beta$ -lactamase fragment fused to a flexible polypeptide linker and first interactor domain,' the reference linker refers to one of the interactor domain of the instant claims; and the  $\beta$ -lactamase fragment is same as the instant claim marker protein (i.e., circularly permuted marker protein); and further the reference claims intended use of the claimed oligopeptide in fragment complementation system which use the circularly permuted  $\beta$ -lactamase. And further the reference claims recite 'an oligopeptide ... consisting essentially of an N-terminal  $\beta$ -lactamase fragment....', the recitation of 'consisting essentially' makes the claim open and may include other peptides or fragments. Thus, the reference oligopeptide is clearly same as the instant claim detector.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### *Conclusion*

23. No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padmashri Ponnaluri  
Primary Examiner  
Art Unit 1639

Pp  
28 April 2004

  
**PADMASHRI PONNALURI**  
**PRIMARY EXAMINER**